PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference GW/G23484WO	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/JP 03/13901	International filing date *(day/month/year)* 30.10.2003	Priority date *(day/month/year)* 01.11.2002
International Patent Classification (IPC) or both national classification and IPC A61K31/381		
Applicant TAKEDA CHEMICAL INDUSTRIES, LTD. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
03.02.2004	01.12.2004
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Elliott, A Telephone No. +49 89 2399-8218

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/JP 03/13901

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-235 as originally filed

Claims, Numbers

1-30 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 1-18,20-29 (all partially)

   because:

   ☒ the said international application, or the said claims Nos. 21-24 relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 1-18, 20-29 (all partially)

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees, the applicant has:

   ☐ restricted the claims.

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ neither restricted nor paid additional fees.

2. ☒ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

   ☒ all parts.

   ☐ the parts relating to claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	3, 9-22, 24-26, 28, 29
	No:	Claims	1, 2, 4-8, 23, 27, 30
Inventive step (IS)	Yes:	Claims	3, 9-22, 24-26, 28, 29
	No:	Claims	1, 2, 4-8, 23, 27, 30
Industrial applicability (IA)	Yes:	Claims	1-20, 25-30 (Claims 21-24 . no opinion)
	No:	Claims	-

2. Citations and explanations

   see separate sheet

The application relates to agents for treating or preventing neuropathy comprising the compounds of formula (I) as defined in the application, agents for promoting the production or secretion of a neurotrophic factor comprising the compounds of formula (I) as defined in the application, agents for ameliorating pain comprising the compounds of formula (I) as defined in the application, neuroprotective agents comprising the compounds of formula (I) as defined in the application, compounds of formula (II) as defined in the application, a pharmaceutical agent comprising the compounds of formula (II), a method for treating or preventing neuropathy in a mammal comprising administering a compound of formula (I) to said mammal, a method for promoting the production or secretion of a neurotrophic factor in a mammal comprising administering a compound of formula (I) to said mammal, a method for ameliorating pain in a mammal comprising administering a compound of formula (I) to said mammal, a method for protecting a nerve in a mammal comprising administering a compound of formula (I) to said mammal, the use of the compound of formula (I) for the production of an agent for preventing or treating neurotrophy, the use of the compound of formula (I) for the production of an agent for promoting the production or secretion of a neurotrophic factor, the use of the compound of formula (I) for the production of an agent for ameliorating pain, the use of the compound of formula (I) for the production of a neuroprotective agent, a method of producing the compounds of formula (II) and a method of producing intermediate compounds of formula (XVI) as defined in claim 30.

The following documents are referred to in this report:

D1: WO 2003 049702 A (AMGEN INC) 19 June 2003
D2: WO 2002 098852 A (PIERRE FABRE MEDICATENT) 12 December 2002
D3: REVISTA PORTUGUESA DE FARMACIA, vol. 49, no. 4, 1999, pages 153-160
D4: RUSSIAN JOURNAL OF ORGANIC CHEMISTRY (TRANSLATION OF ZHURNAL ORGANICHESKO KHIMII), vol. 38, no. 8, 2002, pages 1171-7
D5: WO 2000 075120 A (AGOURON PHARMACEUTICALS INC 14 December 2000
D6: EP-A-1 148 053 (ONO PHARMACEUTICAL CO) 24 October 2001
D7: PATENT ABSTRACTS OF JAPAN vol. 1998, no. 12, 31 October 1998 & JP 10 195063 A (DAI ICHI SEIYAKU CO LTD)
D8: CHEMICAL & PHARMACEUTICAL BULLETIN, vol. 44, no. 5, May 1996, pages 991-999
D9: US-A-5 464 860 (LEPAGE, FRANCIS ET AL) 7 November 1995
D10: US-A-5 250 504 (MARAVETZ, LESTER L.) 5 October 1993
D11: US-A-4 835 280 (MARTENS, ALFRED ET AL) 30 May 1989
D12: YIYAO GONGYE (PHARMACEUTICAL INDUSTRY), vol. 17, no. 10, 1986, pages 444-8
D13: EP-A-0 153 850 (SAWAI PHARMACEUTICAL CO LTD) 4 September 1985
D14: US-A-4 172 136 (BERGER, HERBERT ET AL) 23 October 1979
D15: US-A-3 702 330 (HOFF, DALE R. ET AL) 7 November 1972

D16: JOURNAL OF MEDICINAL CHEMISTRY, vol. 40, no. 20, 26 September 1997, pages 3297-3304
D17: BIOORGANIC & MEDICINAL CHEMISTRY, vol. 4, no. 2, February 1996, pages 227-237
D18: BIOORGANIC & MEDICINAL CHEMISTRY, vol. 9, no. 12, December 2001, pages 3243-3253
D19: BIOORGANIC & MEDICINAL CHEMISTRY, vol. 8, no. 2, February 2000, pages 449-454
D20: JOURNAL OF MEDICINAL CHEMISTRY, vol. 37, no. 15, 22 July 1994, pages 2411-2420

III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

No unified criteria exist under the PCT for assessing the industrial applicability of the subject-matter of claims **21-24** (methods of medical treatment). Hence it is not possible at this stage of the proceedings to give an opinion as to the industrial applicability of these particular claims.

The opinion expressed in this report is additionally not to be considered as complete as the subject-matter of all claims has not been searched for the reasoning set out by the ISA. Hence this report is only to be considered valid for the subject- matter of the present application which relates to compounds according to the application wherein A is as defined in claim 1, groups X, Z and Y together form an acylamide linker and R^1 is a phenylene group.

IV Lack of unity of invention

Lack of unity of invention exists between the subject-matter of claims 1-29 (hereinafter defined as invention 1) and the subject-matter of claim 30 (hereinafter defined as invention 2). Lack of unity exists as the compounds being prepared according to claim 30, which are intermediates in the preparation of the compounds referred to in claims 1-29, are known compounds (cf. documents in the International Search Report which have been cited against claim 30).

V Reasoned statement under Art 35(2) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement

Claims 1-29

(Cf. the comments under III above)

A number of documents in the International Search Report have been cited as category X against claims 1, 2, 4-8 on the grounds that these documents anticipate the subject-matter of these claims. The reasoning is that, although the proposed use

for the compounds of formula (I) is given in claims 1-8, the fact that the proposed use is mentioned in the claim is not sufficient for these claims to be delimited from documents of the prior art which disclose compounds of formula (I) per se. Claims 1, 2, 4-8 therefore lack novelty.

Document D3 discloses compounds having the same use as the present application, namely for the relief of pain. Therefore claims 23 and 27 additionally lack novelty with respect to this document.

The subject-matter of claim 9 and claims dependent thereupon would appear to have been neither disclosed in the prior art nor appear to be suggested thereby. The closest prior art (art from D3) would appear to be represented by a document which the applicant himself cited in the description, namely US-B-6605629, which resulted from PCT application WO-A-01 14372 (1 March 2001). This document describes 5-membered ring heterocyclics and their use as neurotrophin production or secretion promoting agents.

Claim 30

The subject-matter of claim 30 is either not novel with respect to documents D16-D20 or easily derivable therefrom. Articles 33(2) and (3) PCT are not complied with.

Other matters:

1. Documents D1 and D2, published in June 2003 and December 2002 respectively, i.e. in the priority interval of the present application, are not to be considered as prior art according to Rule 64.3 PCT.

   It is, however, already pointed out that the content of D3 may be taken into account in the examination of the patentability of the presently-claimed subject-matter of the present application when the application enters the regional phase of the proceedings depending upon the validity of the priority claimed for the present application and the validity of the priorities claimed for D1 and D2.

   D2 contains disclosures of compounds falling under the scope of claims 1,2,4-8.

   D1 contains disclosures of compounds falling under the scope of claims 1,2,4-8 and additionally the same uses of these compounds as claimed in present claims 21-28.

2. It would appear that reference to D3 should be made in the description. Additionally as the document which is also to be considered closest prior art should be a document to be considered as prior art under Rule 64.3 PCT, reference to US-B-6605629 should be amended to include WO-A-01 14372.